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Words and objects at the tip of the left temporal lobe in primary progressive aphasia

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Eleven of 69 prospectively enrolled primary progressive aphasics were selected for this study because of peak atrophy sites located predominantly or exclusively within the anterior left temporal lobe. Cortical volumes in these areas were reduced to less than half of control values, whereas average volume elsewhere in the left hemisphere deviated from control values by only 8%. Failure to name objects emerged as the most consistent and severe deficit. Naming errors were attributed to pure retrieval failure if the object could not be named even when the denoting word was understood, the object recognized and the two accurately matched. Surprisingly many of the naming errors reflected pure retrieval failures, without discernible semantic or associative component. The remaining set of errors had associative components. These errors reflected the inability to define the word denoting the object more often than the inability to define the nature of the pictured object. In a separate task where the same object had to be linked to verbal or non-verbal associations, performance was abnormal only in the verbal format. Excessive taxonomic interference was observed for picture–word, but not picture–picture, matching tasks. This excessive interference reflected a blurring of intra- rather than inter-category distinctions as if the acuity of word–object associations had been diminished so that correspondences were easier to recognize at generic than specific levels. These dissociations between verbal and non-verbal markers of object knowledge indicate that the reduced neural mass at peak atrophy sites of the left temporal tip, accounting for half or more of the presumed premorbid volume, was unlikely to have contained domain-independent semantic representations of the type that would be expected in a strictly amodal hub. A more likely arrangement entails two highly interactive routes—a strongly left lateralized temporosylvian language network for verbal concepts, and a presumably more bilateral or right-sided inferotemporal/fusiform object recognition network, which remained relatively spared because peak atrophy sites were concentrated on the left. The current results also suggest that the left anterior temporal neocortex should be inserted into the language network where it is likely to play a major role in selecting verbal labels for objects and mediating the progression of word comprehension from generic to specific levels of precision.

Keywords: dementia; semantic; language; naming; frontotemporal

Abbreviations: NOMINA = Northwestern Multidimensional Naming Assessment; PPA = primary progressive aphasia;
PPVT = Peabody Picture Vocabulary Test

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Introduction

The current investigation was initiated to explore the relationship of left anterior temporal cortex to object naming and related language functions. As recently as the 1980s, the backbone of the left hemisphere language network consisted of Broca's and Wernicke's areas, interconnected by the arcuate fasciculus (Benson, 1985). The participation of extrasylvian structures, such as the angular gyrus, supplementary motor area, thalamus, basal ganglia, insula and Brodmann area 37, was acknowledged but thought to exert a subordinate influence on language function. Much has changed since then. Broca's area has kept its classic inferior frontal location but has been subdivided into a complex mosaic of functional specializations (Anwander *et al*., 2007; Xiang *et al*., 2010); the ever-wandering Wernicke's area seems to have shifted its location from the superior to the middle temporal gyrus (Bogen and Bogen, 1976; Booth *et al*., 2002; Ohrui *et al*., 2004; Lau *et al*., 2008; Ogar *et al*., 2011; Turken and Dronkers, 2011; Robson *et al*., 2012); and the arcuate fasciculus has been dissected into direct and indirect components, some of which reach more anterior parts of the temporal lobe than previously envisaged (Catani *et al*., 2005; Rilling *et al*., 2008). The single most drastic evolution in the structure of the language network, however, has revolved around the gradual, but ambivalent, emergence of the left anterior temporal lobe as a potentially critical node for word comprehension and object naming.

Progress in understanding the functions of the anterior temporal lobe has been hampered, at least in part, by the anatomical heterogeneity of this region. Medial aspects of the anterior temporal lobe contain the corticoid, paleocortical and archicortical formations of the amygdala, pyriform cortex and hippocampus. Its lateral, dorsal, ventral and polar aspects provide sites of confluence for the superior, middle and inferior temporal gyri, where the most anterior components of auditory and visual association areas abut intercalated swaths of temporal transmodal neocortices (Morán *et al*., 1987). By the middle of the 20th century, cerebrovascular accidents in the territory of the posterior cerebral artery, uncinate seizures and surgical resections in epileptic patients had started to assign critical roles to the mediolimbic components of the anterior temporal lobe in episodic memory, mood and motivation (Hughlings Jackson and Colman, 1898; Bekhterev, 1900; Terzian and Ore, 1955; Scoville and Milner, 1957). However, the neocortical parts of the anterior temporal lobe remained inaccessible to similar clarifications, principally because of their invulnerability to focal cerebrovascular accidents.

Initial insights into the non-limbic functions of the anterior temporal lobe emerged from investigations of patients with neurodegenerative disease (Snowden *et al*., 1989), head trauma (Kapur *et al*., 1992) and herpes simplex encephalitis (Warrington and Shallice, 1984). The temporal lobe damage in these cases was extensive, almost always bilateral, and included much more than the anterior temporal neocortex. As expected, the patients displayed complex mixtures of amnesia, agnosia and anomia. The resultant combination of verbal and non-verbal deficits in word and object knowledge and their category-specificity were attributed to an erosion of general semantic memory (Warrington and Shallice, 1984).

This line of research gained considerable momentum with the delineation of the semantic dementia syndrome and its linkage to anterior temporal lobe neurodegeneration (Snowden *et al*., 1989; Hodges *et al*., 1992). A rich set of systematic investigations in these patients revealed complex patterns of object anomia and word comprehension deficits (Hodges *et al*., 2000; Jefferies *et al*., 2009). However, the identification of equally severe impairments of non-verbal object representation shifted the focus onto the 'semantic' rather than the 'linguistic' nature of the underlying deficit and led to the conceptualization of the anterior temporal lobe as an amodal hub where verbal and non-verbal attributes of objects were unified without anatomical segregation by domain (Snowden *et al*., 1989; Mummery *et al*., 2000; Bozeat *et al*., 2002; Rogers *et al*., 2004; Patterson *et al*., 2007). The amodal nature of the anterior temporal lobe was further highlighted by an experiment where transcranial magnetic stimulation of either the left or right temporal pole led to combined disruptions of both verbal and non-verbal associative tasks (Pobric *et al*., 2010).

The language-related (i.e. aphasic) manifestations of anterior temporal atrophy attracted renewed attention, as it became clear that many patients with semantic dementia could also be conceptualized as having a fluent form of primary progressive aphasia (PPA) (Mesulam, 2001; Adlam *et al*., 2006; Mesulam *et al*., 2009). Nonetheless, the status of the anterior temporal lobe in the language network remained unsettled for three reasons. First, most of the cases in the literature had relatively extensive and often bilateral temporal lobe atrophy (Hodges *et al*., 1992; Mummery *et al*., 2000; Adlam *et al*., 2006). The question of whether the complex naming and comprehension deficits reflected the impairment of a single semantic system or the combined impairment of the perisylvian language and inferotemporal object recognition networks could therefore not be resolved rigorously (Gainotti, 2012). Secondly, semantic memory, defined as the system that possesses, stores and retrieves information about the meaning of words, concepts and facts (Tulving, 1972; Warrington, 1975), is so inclusive as to preclude its delineation from the 'receptive' functions of the language network. Thirdly, some authors seemed to be reserving the term 'language' to processing of phonology, syntax and morphology but not of word meaning (Bright *et al*., 2008). According to this line of reasoning, loss of word meaning in patients with left temporal lobe atrophy would, by definition, constitute a marker of semantic rather than linguistic impairment.

The current study was initiated to further explore the functions of temporal cortex in a set of patients identified specifically on the basis of peak atrophy sites located either exclusively or predominantly at the tip of the left temporal neocortex. The systematic characterization of object naming failures in these patients helped to address two interrelated questions. What is the role of the anterior temporal cortex in verbal and non-verbal representations of objects? Does it have a selective relationship to language or is it equally important for processing non-verbal concepts? We reasoned that if the left anterior temporal lobe contains an amodal semantic store, verbal and non-verbal deficits in these patients should display comparable severity. If, on the other hand, patients were to display a selective impairment of verbal representations, this part of the brain would need to be considered a component of the distributed language network.

The peak atrophy sites of the patients in the present study were more restricted than those in pivotal studies that have characterized the functional specializations of the anterior temporal lobe (Hodges *et al*., 1992; Mummery *et al*., 2000; Adlam *et al*., 2006). The conceptual framework that guided the study was also more inclusive and defined language as a multifunctional faculty that mediates the encoding as well as decoding of words (Mesulam, 1998). These aspects of language function were investigated with specially designed tests of naming, object-word matching, word comprehension and taxonomic interference. The results revealed unexpectedly heterogeneous mechanisms of anomia in patients with anterior temporal atrophy. When interpreted in the light of additional evidence based on functional imaging, event-related potentials and stroke-induced aphasia, these results also favoured a domain-selective and predominantly linguistic, rather than amodal, role for the left anterior temporal lobe.

Materials and methods

The subjects were identified from a set of 100 patients consecutively referred to the Northwestern University Cognitive Neurology and Alzheimer's Disease Centre for the evaluation of progressive language impairments. The PPA diagnosis was made when three core criteria were met: (i) the presence of a progressive aphasic disorder of recent onset as manifested by gradually intensifying distortions of word usage or comprehension that could not be attributed to more elementary motor or perceptual deficits; (ii) the language impairment constituted the most salient neurobehavioral deficit and the chief impediment to the pursuit of customary daily living activities during the initial stages of the illness; and (iii) diagnostic investigations led to the conclusion that the underlying disease is neurodegenerative (Mesulam, 2001, 2003; Mesulam and Weintraub, 2008). Nineteen of 100 patients did not receive a PPA diagnosis despite the presence of a language impairment because of equally prominent deficits of memory, executive function or comportment; seven patients did not wish to participate in the research project; and five were excluded because of left-handedness. The remaining 69 patients with a PPA diagnosis were prospectively enrolled in a longitudinal investigation that included comprehensive assessment with a uniform testing battery and quantitative structural brain imaging. Eleven of these 69 patients were identified for this study based on statistically significant peak atrophy sites located predominantly in the anterior left temporal lobe as determined by MRI data processed by the FreeSurfer analysis suite. No patient with this atrophy pattern was excluded. Although the patients had been classified into clinical subtypes according to current guidelines (Gorno-Tempini *et al*., 2011), only the anatomy of atrophy determined inclusion into this study.

All participants were Caucasian, native English speakers and right-handed. The study was approved by the Institutional Review Board at Northwestern University, and informed consent was obtained from all participants. Thirty-seven subjects, deemed cognitively unimpaired based on their performance on the Uniform Data Set of the National Alzheimer's Disease Coordinating Centre (Morris *et al*., 2006; Weintraub *et al*., 2009) and additional cognitive tests of language, visuospatial functions and memory, constituted the cognitively normal control group. The Clinical Dementia Rating Scale (Morris, 1993) and the Mini-Mental State Examination (Folstein *et al*., 1975) were used to assess global aspects of functionality and cognition, respectively. The aphasia quotient of the revised Western Aphasia Battery served as a global measure of aphasia severity (Kertesz, 2006).

Specialized tests of language and object knowledge

The revised Western Aphasia Battery was developed for characterizing prominent aphasias in patients with focal—predominantly cerebrovascular—lesions. Many of its subtests are not challenging enough for patients with PPA, especially at early and mild stages of disease. Additional and more specialized tests were therefore used to gauge the integrity of grammaticality, repetition, naming, word comprehension and object knowledge. Grammaticality of sentence production was assessed with the Northwestern Anagram Test (Weintraub *et al*., 2010; Thompson *et al*., 2012) and the Sentence Production Priming Test of the Northwestern Assessment of Verbs and Sentences (Thompson, 2011). Performance on two subsets of 15 non-canonical sentences, one from the Northwestern Anagram Test and another from the Northwestern Assessment of Verbs and Sentences-Sentence Production Priming Test, was averaged to derive a composite score of grammatical sentence production (Northwestern Anagram Test/Northwestern Assessment of Verbs and Sentences), as previously described for the quantitative characterization of PPA subtypes (Mesulam *et al*., 2012).

Speech, as assessed from recorded narrative, was described as fluent, laboured or apraxic. Repetition was quantitated with the six most difficult items from the repetition subtest of the revised Western Aphasia Battery. We previously used performance on this subset (WAB-REP) to classify PPA subtypes at early and mild stages of impairment (Mesulam *et al*., 2012). The Boston Naming Test was used to assess the naming of objects (Kaplan *et al*., 1983). Single word association and comprehension was tested with a subset of 36 moderately difficult items (157–192) of the Peabody Picture Vocabulary Test (PPVT), fourth revision (Dunn and Dunn, 2006). Performance on this particular set of items had been used to construct a quantitative template for subtyping PPA and has become a core component of our testing battery (Mesulam *et al*., 2009). Each item requires the patient to match an auditory word representing an object, action or attribute to one of four picture choices. Although the PPVT-IV is a word–picture matching task, less than half of the items represent concrete objects. The majority of the remaining words (e.g. salutation, perplexed, culinary) require extensive associative interpretation (i.e. comprehension) of the words in order to match them to pictorial representations of the corresponding concept. Surface dyslexia and dysgraphia were examined with selected examples of exception words from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Kay, 1992) and scored as previously described (Mesulam *et al*., 2012). Object knowledge was assessed with two non-verbal tasks of thematic associations. In the three-picture version of the Pyramids and Palm Trees Test (Howard and Patterson, 1992), the patient is asked to decide which of two black-and-white line drawings of objects is thematically more closely associated with a target object. The test contains 52 triplets. Additionally, object knowledge was quantitated by a task of context matching we designed where the subject is asked to determine whether pairs of realistic colour photographs of objects, presented on a computer screen, depicted thematic matches (e.g. cooking thermometer/turkey) or mismatches (e.g. plunger/camera). There were 74 such pairs and the subject was asked to press one button if the two objects 'are usually seen or used together' and another button if not. To control for differently scaled variables in all measures, quantitative performance scores were transformed into a percentage of the total possible score.

NOMINA

We designed the Northwestern Multidimensional Naming Assessment (NOMINA) to resolve each naming event into five principal components: the naming of the object, the verbal definition of the object, the verbal definition of the word denoting the object, the matching of the word to the object and the chronometric assessment of taxonomic interference. Naming failures can be associated with different patterns of impairments in these five components, each pattern revealing a potentially different underlying mechanism. The full NOMINA contains 40 line drawings of common objects and 40 written words corresponding to their names. They are evenly divided into four categories, two of artefacts (tools and clothes) and two of natural kinds (animals and fruits/vegetables). Test forms A and B each contain line drawings of 20 of the objects, five of each category, intermingled as to category but regularly spaced into four rows and five columns on an 8.5 × 11 inch sheet of laminated paper. Test forms C and D each contained the names of the objects in forms A and B, respectively, written on a sheet of the same size and spatially arranged in the same fashion as the drawings (Mesulam *et al*., 2009).

The patients were first shown object drawings, one at a time, and asked to name them and describe their use or nature. They were then asked to read aloud the words, presented one at a time, and define them verbally. The object and word definitions were recorded. Patients were next administered the four forms of the matching tests, in an ACDB order. In forms A and B (word–picture matching), the subject was given a card with a single word on it and asked to point to the matching object on the test form. In forms C and D (picture–word matching), the subject was shown a single object picture and had to point to the matching word on the test form. Two raters (M.M. and C.W.) listened to the recorded definitions and scored them on a scale previously developed for characterizing anomias in PPA (Mesulam *et al*., 2009); 0 = clearly wrong, irrelevant or 'don't know'; 1 = low taxonomic precision in describing the nature or use of the target item (e.g. 'you eat it', 'you wear it', 'animal', or 'you use it'); 2 = medium taxonomic precision (e.g. 'dessert', 'guys wear it', 'large animal in Africa' or 'use it for cooking'); 3 = high taxonomic precision (names the picture correctly or provides a description that is relatively unambiguous, e. g. for strawberry, 'It is sweet, red and I put it in my cereal'; for tie, 'guys wear it around the neck'; for cat, 'cute animal around the house that is self-absorbed'; and for broom, 'use it to sweep the floor').

Each word and each picture was presented only once during the word-to-picture and picture-to-word matching tasks. The set of stimuli in test forms A (drawings) and C (written words) were as follows: socks, belt, tie, vest, glove, brush, stapler, spatula, funnel, broom, onion, corn, pepper, radish, celery, mouse, squirrel, frog, snake and cat. In forms B (drawings) and D (written words), the stimuli were as follows: dress, coat, shirt, hat, shoe, hammer, pliers, saw, scissors, screwdriver, apple, grapes, strawberry, pear, pumpkin, elephant, hippopotamus, zebra, lion and camel. The stimuli were taken from the Northwestern Naming Battery, a comprehensive naming test designed to test lexical processing deficits in aphasia (Thompson *et al*., 2012). There were no significant differences of word length, familiarity or frequency when names of living objects (animals and fruits/vegetables) were compared with names of non-living objects (clothing, tools) [mean and standard deviation (SD) of 5.65 ± 1.66 versus 5.60 ± 2.19 for length; 3.27 ± 0.87 versus 3.73 ± 0.55 for familiarity; 14.45 ± 15.9 versus 26.17 ± 30.7 for frequency using the CELEX database] (Baayen *et al*., 1993). Five patients were given the full NOMINA; the others were tested with the 20 items in forms B and D.

The 40 object/word pairs of NOMINA were also used for the chronometric assessment of taxonomic interference. The patient heard a word and 400 ms later saw side-by-side pictures of two different objects on a computer screen. One picture (target) depicted the object designated by the spoken word, the other (distracter) did not. Targets and distracters were equally placed on the right and left side of the screen. There were 40 pairs, 20 with natural kinds as targets and 20 with artefacts as targets. Each word was presented only once. Each drawing was presented twice, once as the target and once as the distracter. In half the trials, the distracter and target belonged to the same one of the four categories (i.e. clothing, tools, animals, fruits/vegetables). The subject was asked to press the computer key on the side of the object matching the stimulus word as quickly as possible, and reaction times were recorded. There were no significant differences of length, familiarity or frequency in the target words used for trials of semantically related versus unrelated pictures (mean and SD of 5.65 ± 1.92 versus 5.55 ± 1.92 for length; 3.54 ± 0.08 versus 3.50 ± 0.08 for familiarity; 20 versus 20 for frequency in the CELEX database).

Taxonomically Graded Object Association Task

We designed this task to examine the impact of taxonomic distance on the detection of verbal and non-verbal associations of pictured objects. Stimuli were 48 concrete nouns and 48 photographs of the corresponding objects. The items were of lower frequency than those used for the NOMINA [average log CELEX frequency of 0.31 (SD = 0.33)], (Baayen *et al*., 1993). Each trial consisted of a prime (always a picture) followed by a probe (picture or word). Congruity between primes and probes was manipulated such that they matched in half of trials but not in the other half. The match consisted of the word denoting the object (in picture–word trials) or a different exemplar of the same object (in picture–picture trials). The mismatches could be taxonomically related (e.g. pear for pineapple) or unrelated (hammer for pineapple). Stimuli were counterbalanced such that each item appeared as a matching, related and unrelated probe in both the word and picture platforms. Participants were asked to press one button on matching trials and another button for mismatched trials, whether taxonomically related or unrelated. The interval between trials randomly varied between 2.5 and 3.5 s. Additional details of the task are given in Hurley *et al*. (2012).

Structural magnetic resonance imaging

In all cases, imaging was obtained within 72 h of the cognitive testing. Structural MRI scans were acquired on a 3-T Siemens TRIO using an MP-RAGE sequence and reconstructed with the FreeSurfer image analysis suite (version 4.5.0) as previously described (Mesulam *et al*., 2009; Rogalski *et al*., 2011) for every participant in the Northwestern PPA Research Programme. Cortical thickness maps of each individual patient with PPA were statistically contrasted against 27 right-handed age- and education-matched healthy volunteers. Differences in cortical thickness between groups were calculated by conducting a general linear model on every vertex along the cortical surface. False discovery rate (FDR) was applied at 0.01 to adjust for multiple comparisons and to detect areas of peak cortical thinning (i.e. atrophy) in patients with PPA compared with control subjects (Genovese *et al*., 2002). In each patient, the FreeSurfer analysis suite was additionally used to compute cortical volume within the area bounded by the left anterotemporal peak atrophy site (e.g. area demarcated by the continuous red and yellow patch in the heat maps of Figs 1–3). Volume within areas corresponding to each of these 11 peak atrophy maps was also computed in the control subjects. A second set of volumes was computed for the remaining parts of the left hemisphere of patients and controls. The differences between corresponding values in patients and controls were used to infer the amount of cortical volume that was lost to the underlying neurodegenerative process. Measurements were adjusted for intracranial volume of each subject (Buckner *et al*., 2004).

Statistical analyses

Data are reported as mean ± SD. Age, years of education and test scores were compared between PPA and control groups using the independent sample *t*-test. Reaction times were analysed using repeated measures analysis of variance (ANOVA). Accuracy comparisons in the NOMINA were analysed with the Wilcoxon Signed Ranks Test. Performance in the Graded Object Association Task was analysed by *t*-test and analysis of variance. Statistical significance was indicated if $P < 0.05$ or if outside the 95th percentile of the control range.

Results

The only common denominator in Patients S1–S11 was the location of the most conspicuous peak atrophy site at the tip of the left temporal lobe (Figs 1–4). In Patients S1, S3, S4, S6, S7 and S8, there were no other peak atrophy sites. In the other subjects, additional, but much smaller, peak atrophy sites were also identified in other regions, including the tip of the right temporal lobe in Patients S2, S9–S11, and left temporoparietal junction in Patient S5. In all patients, peak atrophy in the left temporal lobe encompassed the temporopolar cortex as well as the anterior tips of the superior, middle and inferior temporal gyri. On the medial surface, the anterior parahippocampal and fusiform gyri displayed conspicuous peak atrophy sites in only some of the patients. Even in subjects with very circumscribed areas of atrophy (e.g. Patient S1), the cortical ribbon of the left anterior temporal cortex displayed pronounced thinning (Fig. 4). Cortical thinning was markedly greater in the left hemisphere even in patients with contralateral right temporal lobe atrophy (e.g. Patient S11 in Fig. 4). Within the left anterior temporal area of peak atrophy, cortical volumes were 53–64% under control values, a difference that was attributed to the disease-induced loss of neural tissue (Table 1). Volume in the remaining parts of the left hemisphere differed from control subjects by only 0–16%, illustrating the distinct (but not necessarily absolute) sparing of areas outside the region of peak atrophy.

Age and education in the PPA group were not significantly different from the control group (Table 2). Symptom duration ranged from 2 to 11 years. The Clinical Dementia Rating Scale sum of boxes in the subjects with PPA ranged from 0.5 to 4, on a scale where 0 is intact and 18 most impaired. Average Mini-Mental State Examination score in the patient group was

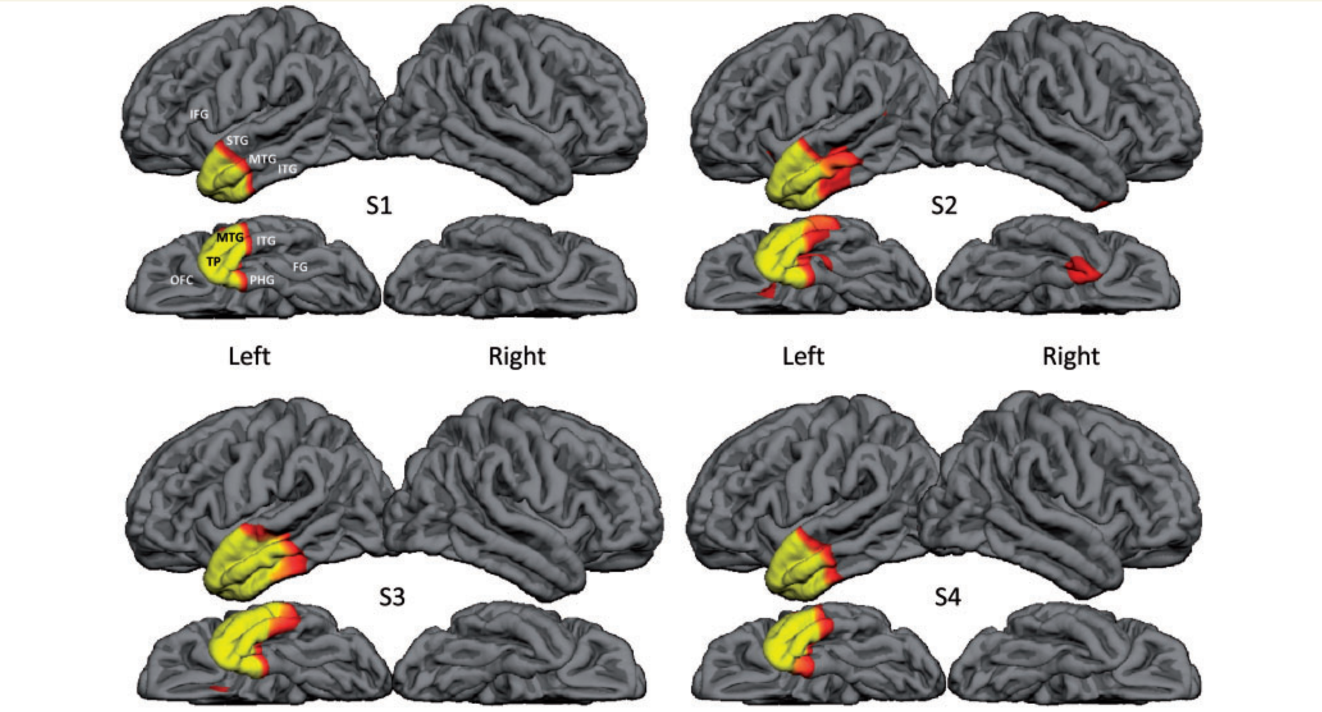

Figure 1 Peak atrophy sites in Patients S1–S4. Yellow and red indicate areas of significant thinning (atrophy) compared with normal control subjects, with a false discovery rate (FDR) of 0.01. FG = fusiform gyrus; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; OFC = orbitofrontal cortex; PHG = parahippocampal gyrus; STG = superior temporal gyrus; TP = temporopolar cortex.

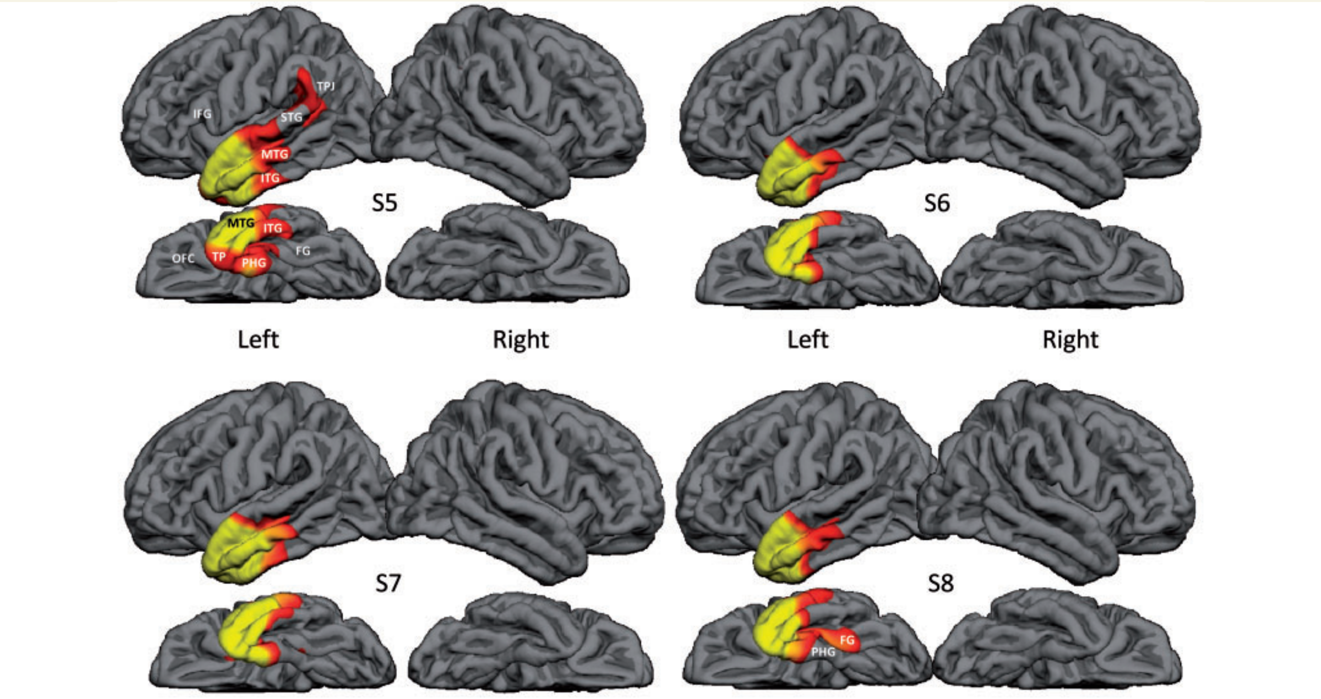

Figure 2 Peak atrophy sites in Patients S5–S8. Yellow and red indicate areas of significant thinning (atrophy) compared with normal control subjects, with a false discovery rate (FDR) of 0.01. FG = fusiform gyrus; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; OFC = orbitofrontal cortex; PHG = parahippocampal gyrus; STG = superior temporal gyrus; TP = temporopolar cortex; TPJ = temporoparietal junction.

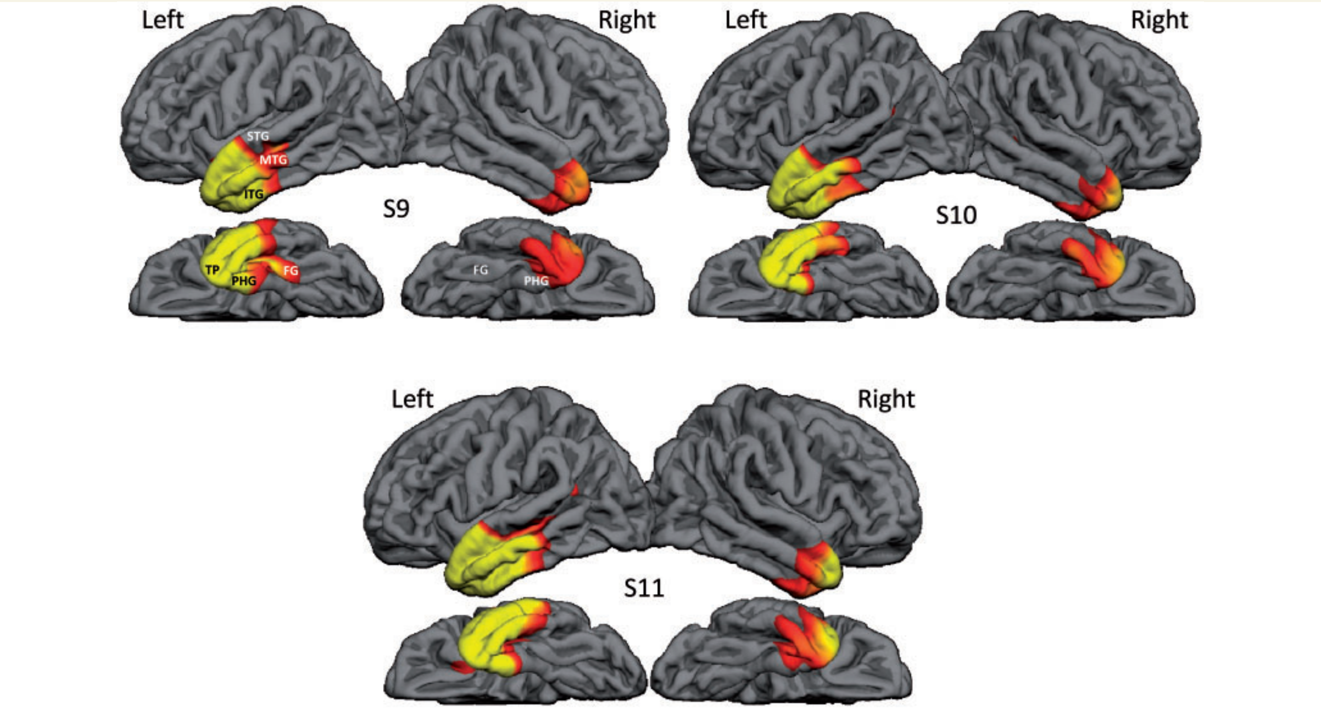

Figure 3 Peak atrophy sites in Patients S9–S11. Yellow and red indicate areas of significant thinning (atrophy) compared with normal control subjects, with a false discovery rate (FDR) of 0.01. FG = fusiform gyrus; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; OFC = orbitofrontal cortex; PHG = parahippocampal gyrus; STG = superior temporal gyrus; TP = temporopolar cortex.

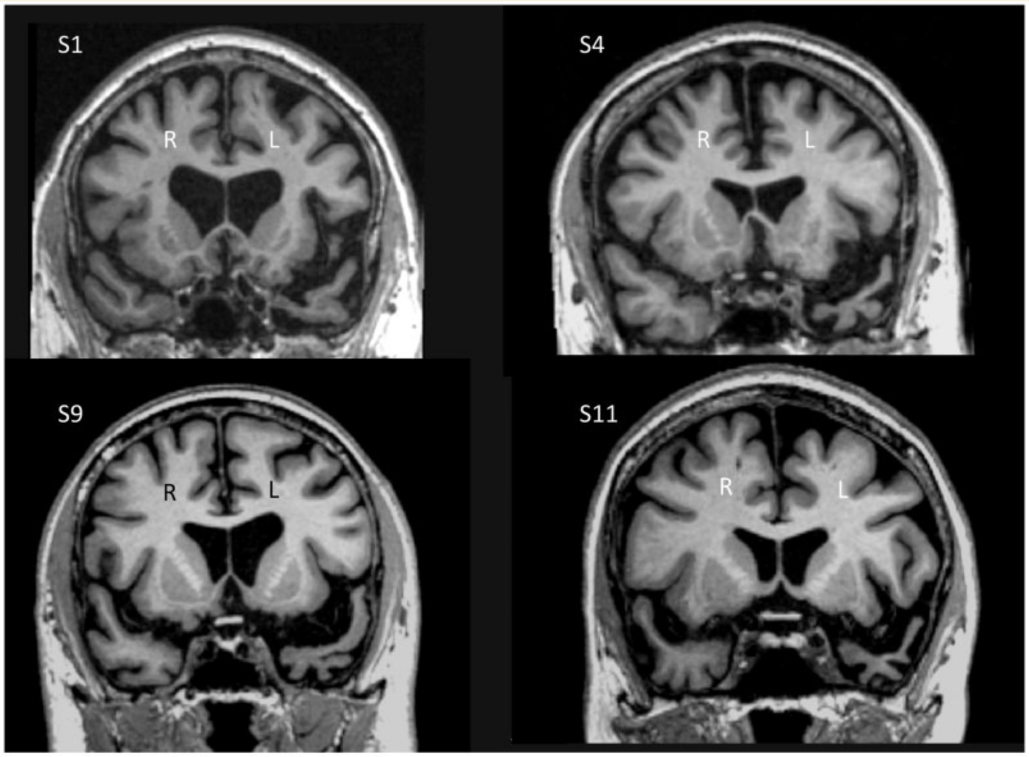

Figure 4 Coronal magnetic resonance scans through the anterior temporal lobes in four of the patients. Even Patient S1, who has the least overall atrophy and mildest anomia, has distinct atrophy on the left. In Patients S9 and S11, who have spread of atrophy to the right hemisphere, the asymmetry is still prominent. Patient S11 is the one case where thinning of the anterior temporal cortex on the right is clearly identifiable. L = left; R = right.

Table 1 Cortical volumes

Case	Volume loss at peak atrophy sites of left anterior temporal lobe (%)	Volume loss elsewhere in left hemisphere (%)
S1	59	7
S2	59	6
S3	59	9
S4	56	13
S5	53	15
S6	57	8
S7	58	7
S8	54	4
S9	64	8
S10	58	0
S11	64	16

The differences between corresponding values in patients and control subjects were used to infer the percentage of cortical volume that was lost to the underlying neurodegenerative process.

Table 2 Sample characteristics

Case	Age/ gender	Education years	Symptom duration (years)	CDR SOB	MMSE total
S1	69/M	18	3	2.5	30
S2	55/F	16	3	2.5	29
S3	54/M	20	2	1.0	28
S4	64/M	20	5	1.0	25
S5	63/M	17	11	4.0	24
S6	61/F	13	2	1.5	24
S7	56/F	18	2.5	4.0	23
S8	54/F	12	3	0.5	27
S9	63/M	18	5.5	4.0	27
S10	54/F	16	4.5	3.0	22
S11	55/F	18	3.5	3.5	25
NC ($n = 37$)	62.2 ± 7	16 ± 2		0	29 ± 0.7

CDR = Clinical Dementia Rating Scale; MMSE = Mini-Mental State Examination; NC = control subjects; SOB = sum of boxes.

25.8 of a total 30 points. Global cognition and functionality were therefore mostly preserved.

The control group performed at almost ceiling levels in all tested domains (Table 3). The determination of selectively impaired versus relatively spared domains in PPA varies according to overall aphasia severity. A template-based quantitative approach recommended the use of flexible cut-off scores flanked by a grey zone of uncertainty, with the cut-off level being based on the overall severity of aphasia in the sample (Mesulam *et al*., 2012). The overall aphasia severity of the patients in this study was at a level intermediate between two previously reported samples, in which cut-off performance scores of 90% (for a group of very

Table 3 Scores on tests of language and object knowledge

Subject	WAB AQ	Grammar NAT/NAVS	Repetition WAB-REP	Naming BNT	Word association/ comprehension PPVT	Non-verbal object knowledge	
						PPTpict	Context Match
PPA mean (SD)	84.2* (7.8)	88.3 (18.5)	84.4* (15)	23.1* (21.9)	52.5* (25)	85.1* (7.4)	88.2* (8.0)
NC mean (SD)	99.7 (0.7)	99.1 (2.4)	98.6 (2.8)	97.2 (3)	98.1 (3.4)	97.9 (2.1)	98.1 (2.2)

All scores are given as percentages of possible total scores for each measure.
Asterisks indicate significant ($P < 0.05$) differences between the means of control and PPA. Scores $\geqslant$80% indicate relatively preserved performance.
BNT = Boston Naming Test; NAT/NAVS = Northwestern Anagram Test and Northwestern Assessment of Verbs and Sentences; NC = control subjects; PPTpict = Pyramids and Palm Trees picture Test; WAB AQ = aphasia quotient of the Western Aphasia Battery; WAB REP = score on a subset of the six most difficult items in the repetition subtest of the WAB.

mildly impaired patients) and 60% (for a group that included severely impaired patients) were used (Mesulam *et al*., 2009, 2012). Accordingly, a cut-off performance score of 75%, flanked on either side by a grey zone of 5%, was chosen to interpret the relative status of the various functional domains in this sample. Performance >80% was considered relatively spared and performance <70% definitely abnormal (Table 3).

Subtypes

Speech quality and surface dyslexia/dysgraphia are among the factors that need to be considered in the classification of PPA (Gorno-Tempini *et al*., 2011). Patient S1 was the only case with laboured apraxic speech. In the absence of word comprehension and object knowledge impairments, Patient S1 would have been classified as having non-fluent/agrammatic PPA by the Gorno-Tempini *et al*. (2011) criteria despite the absence of agrammatism. An implementation of these guidelines in a sample of mildly impaired patients recommended a revision of this practice so that the 'agrammatic' label would not be used without definite agrammatism (Mesulam *et al*., 2012). According to this alternative approach, Patient S1 would be classified as having an anomic form of PPA. Based on the assumption that relatively spared performance needs to exceed 80%, Patients S2, S6, S8 and S9 were classified as having semantic PPA, and Patients S5, S10 and S11 as having mixed PPA (Gorno-Tempini *et al*., 2011; Mesulam *et al*., 2012). Patient S7 fulfilled the core criteria for semantic PPA but fell just short of meeting the ancillary criteria and was therefore unclassifiable. Patients S3 and S4 most closely fit the anomic subtype of PPA (Mesulam *et al*., 2012). These three patients (Patients S3, S4 and S7) were likely to be at prodromal stages of semantic PPA (Mesulam *et al*., 2012). Because the goal of this study was to investigate the consequences of left anterior temporal lobe atrophy, which was the only feature common to all 11 patients, the heterogeneity of the subtypes does not influence the interpretation of the results.

Group and individual performance patterns

The mean group performance of relative sparing and impairment is shown in Fig. 5. It reveals a group pattern of severe anomia and somewhat less severe word association and comprehension impairment on a background of relatively preserved grammaticality, repetition and object knowledge. As neurologically intact control subjects performed at ceiling levels, PPA group performance means were significantly below control values ($P < 0.05$ by *t*-test) in all tested domains except grammar (Table 3).

Performance patterns for individual patients are shown in Figs 6 and 7. Naming was the most impaired domain in 10 of the 11 patients, and the only area of definite impairment in Patient S1, S3 and S4. The impairment was least severe in Patients S1 and S2 who named 68% and 62% of the items, respectively. Considering their Western Aphasia Battery aphasia quotients of 97 and 95, even these Boston Naming Test scores reflect prominent and selective impairment in naming on a background of very mild aphasia. In the other nine subjects, naming was dramatically impaired as reflected by Boston Naming Test scores of 25% or lower. Word association and comprehension, as measured by the PPVT, was the next most pronounced and widespread impairment, with scores of 50% or less in all but three of the subjects (Patients S1, S3 and S4). Neither of the non-verbal object recognition tests (Pyramids and Palm Trees pictures and the Context Matching Test) revealed impairments that were as severe as those of naming and word comprehension. Except for Patients S2 and S11, all non-verbal object association test scores were >80%. Only Patient S11 had <80% accuracy in both object knowledge tasks. In five of the patients (Patients S1, S3, S4, S8 and S9), performance in at least one of the two object knowledge tests displayed accuracies >90%. Upon specific questioning of caregivers and informants, none of the 11 patients were found to have difficulties in interacting with objects or appliances in daily life. Three patients had prominent impairments of grammaticality (Patients S5, S10 and S11) and two patients had prominent impairments of repetition (Patients S5 and S10). In summary, the individual patterns consistently revealed a disproportionately greater impairment on tasks of naming and word associations than on tasks of non-verbal object associations.

Variety of naming failures revealed by the NOMINA

The NOMINA method we designed offers a flexible platform that can be populated by item sets of variable difficulty. In the current study, relatively simple and familiar words were used to avoid floor effects in subjects with severe naming impairments. As expected, naming success rate in the NOMINA was higher than in the

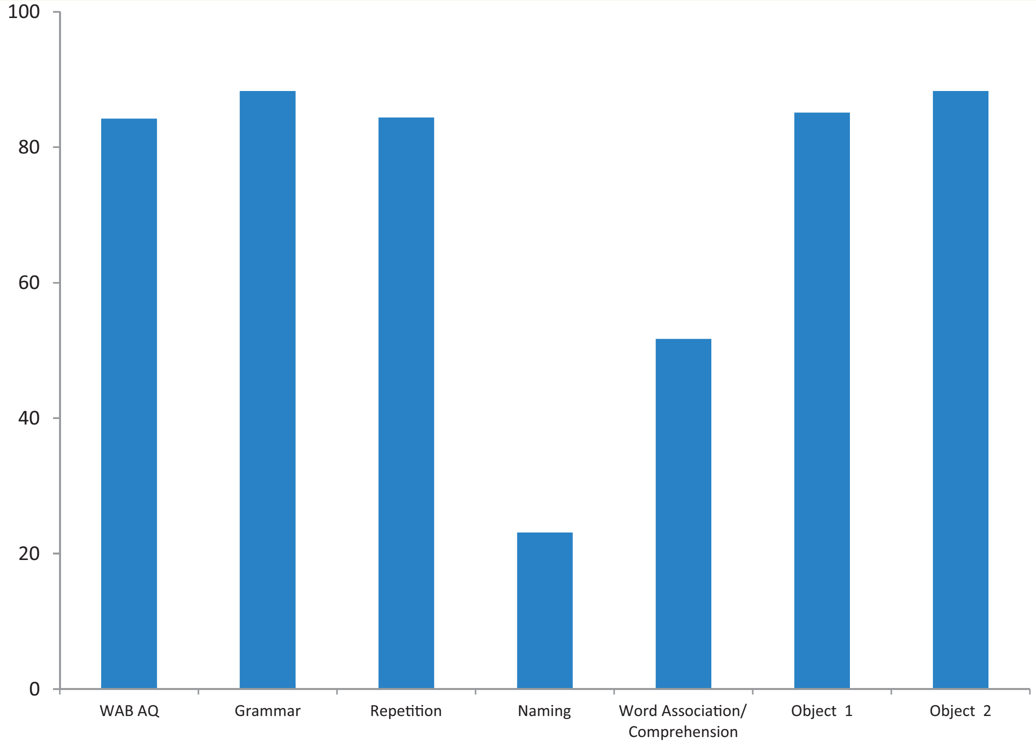

Figure 5 Group performance of patients with PPA. Performance is expressed as percentage of total possible score. Grammar was assessed with the Northwestern Anagram Test and the Sentence Production and Priming Test of the Northwestern Assessment of Verbs and Sentences; repetition with a subset of the six most difficult items in the repetition subtest of the Western Aphasia Battery; naming with the Boston Naming Test; word association/comprehension with a subset of the PPVT; object (knowledge) 1 with the picture form of the Pyramids and Palm Trees Test; object (knowledge) 2 with the Context Matching Test. Means and standard deviations are shown in Table 3. WAB AQ = aphasia quotient of the Western Aphasia Battery.

Boston Naming Test for all subjects and ranged from 100 to 28%. Phonemic paraphasias were rare and those that were close to the target (e.g. 'zion' for 'lion') were not counted as errors. Most failures to name consisted of an incorrect word (frequently a semantic paraphasia) or an 'I don't know' response. Naming errors in NOMINA can be further grouped according to performance on the matching tasks and the precision of word and picture definitions. Matching was considered successful only if it was accurate in both the word–picture and picture–word formats. An error in either format was considered a match failure. Definitions were considered accurate only if they received the highest precision score of 3 and inaccurate if they received scores of 0 or 1. Word or object definitions that received a score of 2 (accurate only at the superordinate level) were deemed too ambiguous and were therefore not used in the classification of anomia patterns.

There were 140 naming errors in the group as a whole, 75 for pictures of natural kinds and 65 for artefacts. Errors were grouped according to the pattern of success or failure in three independent task components: picture–word matching, description of the nature of the object and definition of the corresponding word. Table 4 shows the frequency of three different patterns of naming errors. Group A included naming errors for items on which word-to-picture and picture-to-word matches were both accurate and where words and pictures were defined with precision (i.e. received a score of 3). The assumption was made that the naming errors in Group A represent pure lexical retrieval (or access) impairments, because the word was accurately recognized as the name of the object during matching and also word and object concepts were preserved as reflected by accurate verbal definitions. The proportion of total naming errors that could be attributed to this mechanism varied from subject to subject, without a clear relationship to atrophy patterns. Even in three of the most anomic subjects (Patients S7–S9), more than a third of naming failures fell into this category.

All naming failures that did not fall into Group A had associative components as shown by inaccuracies in definitions and/or matching. Several patterns of such associative anomias are theoretically possible. For example, a naming error for an item that cannot be matched to its name despite the accurate definition of the corresponding word and picture would presumably reflect naming failures specifically due to an interrupted interface between the language and object networks. Such anomic errors, described in the rarely encountered clinical syndrome of optic aphasia, were also rarely encountered in the NOMINA tasks and are not shown in Table 4. A total of only eight such errors could be identified in the entire group of 140 naming failures. Four of these pure interface errors were detected in Patient S7, where they accounted for 14% of the naming failures.

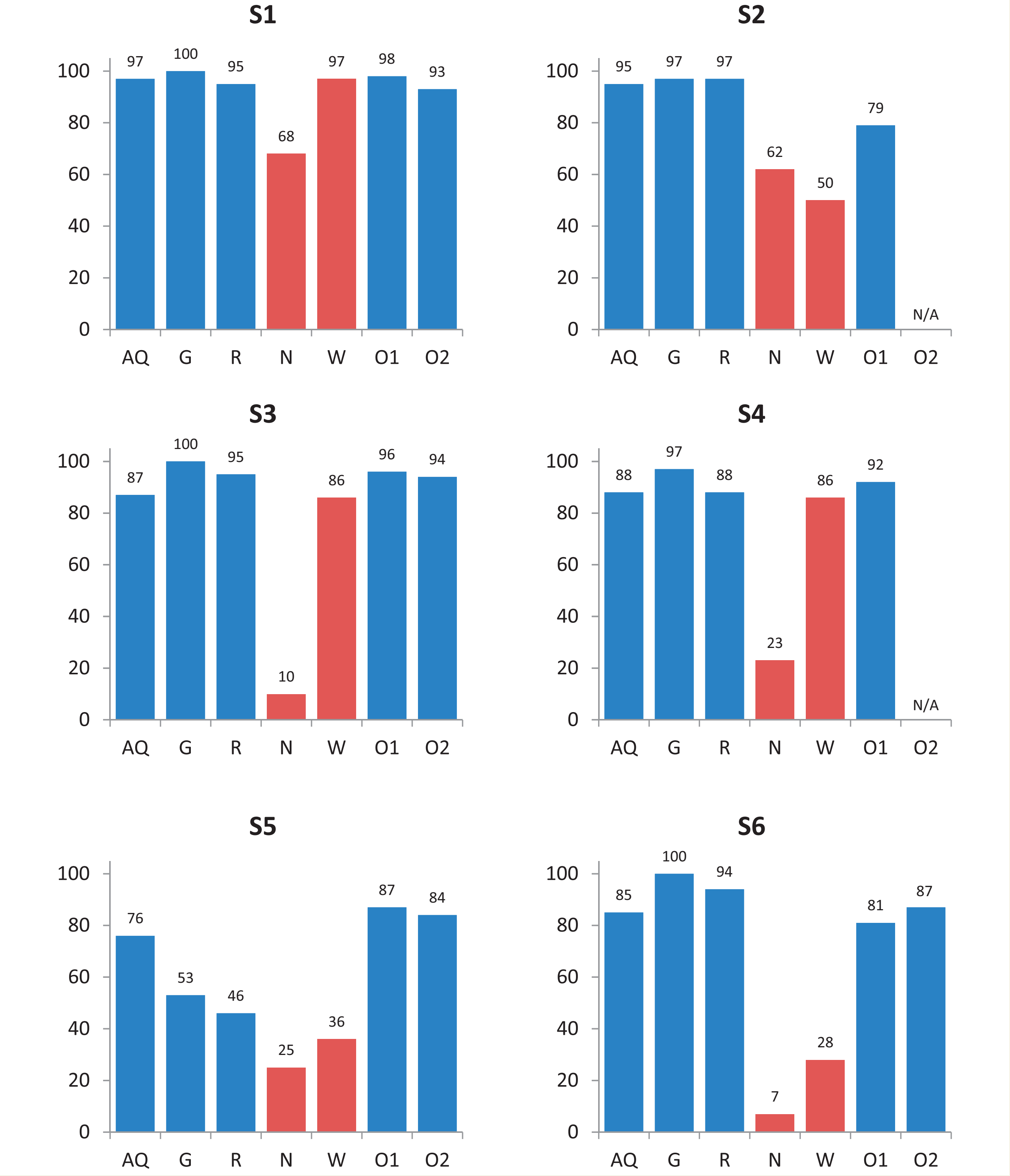

Figure 6 Individual subject (Patients S1–S6) performances expressed as percentage of maximum possible score. AQ = aphasia quotient of the Western Aphasia Battery; G = grammaticality as assessed by the Northwestern Anagram Test and the Sentence Production and Priming Test of the Northwestern Assessment of Verbs and Sentences; N = naming as assessed by the Boston Naming Test; NA = not available; O1 = object knowledge assessed by the picture form of the Pyramids and Palm Trees Test; O2 = object knowledge assessed by the Context Matching Test; R = repetition as assessed by a subset of the six most difficult items in the repetition subtest of the Western Aphasia Battery; W = word association/comprehension as assessed by a subset of the PPVT.

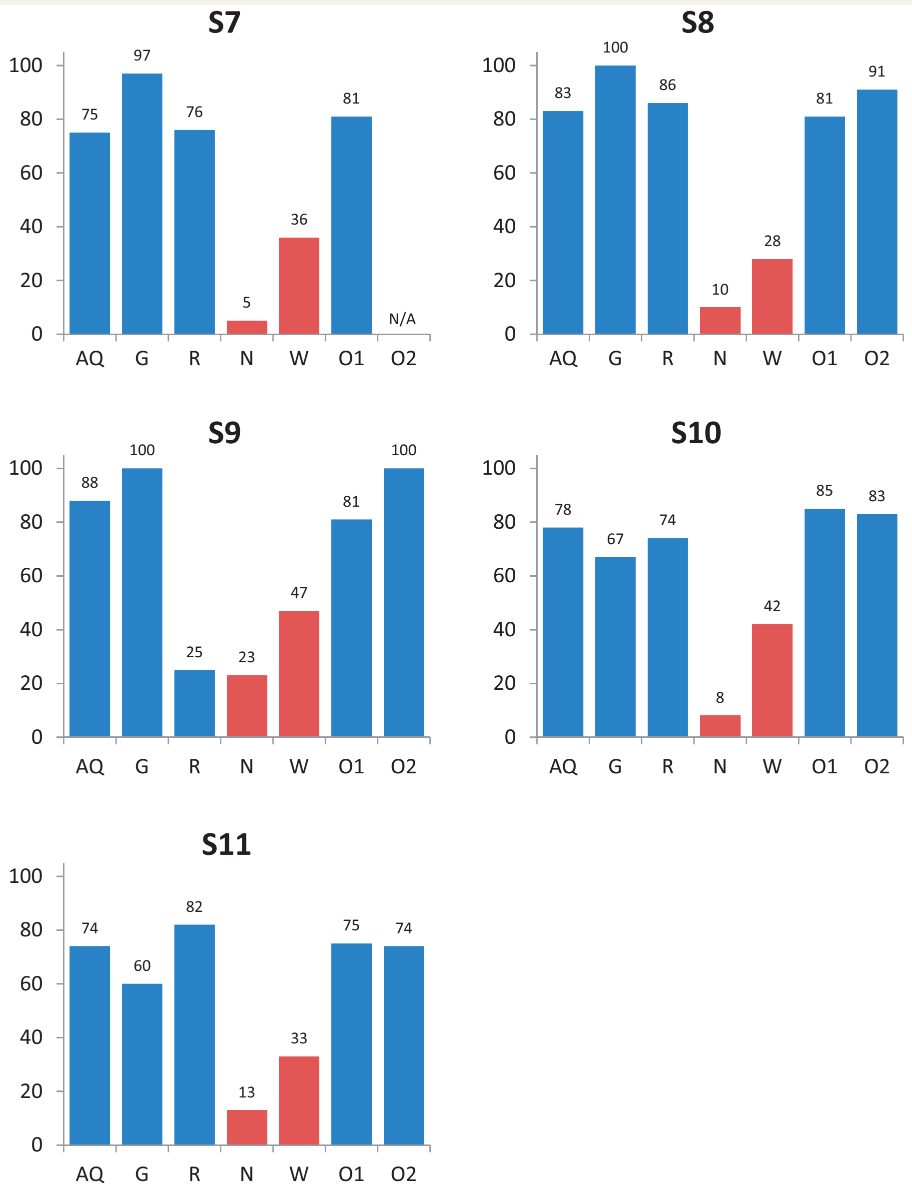

Figure 7 Individual subject (Patients S7–S11) performances expressed as percentage of maximum possible score. AQ = aphasia quotient of the Western Aphasia Battery; G = grammaticality as assessed by the Northwestern Anagram Test and the Sentence Production and Priming Test of the Northwestern Assessment of Verbs and Sentences; N = naming as assessed by the Boston Naming Test; NA = not available; O1 = object knowledge assessed by the picture form of the Pyramids and Palm Trees Test; O2 = object knowledge assessed by the Context Matching Test; R = repetition as assessed by a subset of the six most difficult items in the repetition subtest of the Western Aphasia Battery; W = word association/comprehension as assessed by a subset of the PPVT.

Many of the associative anomic errors occurred for items where the corresponding picture or word could not be defined accurately (Groups B and C of Table 4). Of the nine patients who had all sound files available, only one showed a higher incidence of picture versus word definition failures, a difference based on only a single anomic error. In the five most anomic patients (Patients S6–S10), the percentage of anomic errors associated with word definition failures was higher than the percentage associated with object definition failures. The Wilcoxon Signed Ranks Test showed the difference between Groups B and C to be significant and confirmed the hypothesis that word comprehension impairments have a greater impact on the anomia of these patients than object knowledge impairments ($P < 0.05$, one-tailed). In some patients, such as Patients S8–S10, the greater number of word versus object definition errors associated with unnamed items was pronounced. In others, it was more subtle. Anomic errors that fell into Groups B and C occurred in conjunction with the additional presence of matching failures in 76% and 71% of the items, respectively, illustrating the sensitivity of matching performance to the integrity of word and object concepts as assessed by the accuracy of verbal definitions.

Table 4 Performance on the NOMINA

Case	Total anomic errors (% success)	Group A: anomia with successful matching and definitions (%)	Group B: anomia with picture definition failure (%)	Group C: anomia with word definition failure (%)	Within category matching errors	Taxonomic Interference Index: $(RT_r - RT_u)/RT_u$
S1	0/20 (100)				0/0	0.075
S2	2/40 (95)	100	0	0	0/0	0.112
S3	4/20 (80)	NA	NA	0	1/1	0.149
S4	9/20 (55)	56	11	0	0/1	0.066
S5	10/40 (75)	NA	NA	10	1/1	0.082
S6	13/20 (35)	8	31	46	4/4	0.318*
S7	29/40 (28)	31	34	45	20/26	0.597*
S8	28/40 (30)	32	4	25	24/25	0.832*
S9	25/40 (38)	52	4	20	6/7	0.378*
S10	12/20 (40)	8	0	42	6/6	0.639*
S11	8/20 (60)	25	12	12	0/0	0.498*

The 140 anomic errors were grouped according to success/failure on matching and definition tasks. Group A represents the percentage of all naming errors classified as retrieval anomias. The remaining (i.e. associative) anomias could be classified into many overlapping groups. Two of the most frequently encountered were linked to object definition failures (Group B) and word definition failures (Group C). Within category matching errors designate pointing errors to objects (or words) of the same taxonomic category in the course of word–object and object–word matching trials. An asterisk indicates a value beyond the 95th percentile for the control group.

Taxonomic interference patterns in NOMINA and the Graded Object Association Task

There were 71 matching errors in the entire subject group. In 62 of these (84%), the mispointing involved an item of the same taxonomic category (Table 4, column 6), indicating a blurring of intra-category taxonomic distinctions. In order to clarify the potential mechanisms for this phenomenon, its magnitude was probed with the NOMINA platform, using the same set of objects and words as in the naming and matching tasks.

As noted above, subjects in this test heard a noun and pressed one of two buttons to indicate which of two side-by-side object pictures corresponded to the noun. In half of the trials (related trials), the two pictures belonged to the same taxonomic category, in the other half they represented different categories (unrelated trials). A small number of trials, with reaction times >1.5 times the interquartile range, were designated outliers and excluded from analysis. The average number of excluded trials was 1.45 per PPA subject and 1.09 per control subject, with no significant group differences. In the controls, the reaction time was 807 ± 230 ms for related trials and 712 ± 174 ms for unrelated trials. In the PPA group the reaction time was 1827 ± 1195 ms for related trials and 1355 ± 878 ms for unrelated trials.

The reaction times were significantly slower for related than unrelated trials in both groups ($P < 0.0001$), indicating the presence of taxonomic interference in controls as well as patients. The magnitude of taxonomic interference was determined by dividing the difference of mean reaction times (RT) in related (r) versus unrelated (u) trials by the mean reaction times of unrelated trials: $[(RT_r - RT_u)/RT_u]$. The denominator was introduced to control for individual differences in overall reaction times. In the 21 control subjects, this equation yielded a mean taxonomic interference index of 0.136 with the 95th percentile at 0.285. The taxonomic interference index for Patients S6–S11 exceeded this value and ranged from 0.318 to 0.832. These patients were considered to display abnormally high vulnerability to interference (Table 4). One potential consequence of excessive interference is to blur intra-category distinctions and therefore undermine the specificity of object naming and word comprehension. The reaction times for related trials were classified into those with natural kinds (animals, fruits and vegetables) and artefacts (clothing and tools). None of the subjects showed a significantly different interference effect for one or the other of these two broad categories.

The domain selectivity of this excessive taxonomic interference effect was further assessed with the Graded Object Association Task (Fig. 8). In the non-verbal picture–picture format of this task, an object picture was followed by another exemplar of the same object, by a taxonomically related object, or by a taxonomically unrelated object. In the picture–word format, the same object picture was followed by a noun denoting the object, a noun denoting a taxonomically related object, or a noun denoting a taxonomically unrelated object. The subject was to press one button if there was a match and another if there was a mismatch, whether related or unrelated. Data on this task were available for seven patients (Patients S1–3, S5, S6, S10 and S11) and 23 control subjects. A mixed-model ANOVA Group × Format (pictures versus words) by taxonomic relatedness interaction was significant [$F(2,56) = 8.15$, $P = 0.001$], suggesting that relatedness effects in patients were influenced by the stimulus format. *Post hoc* *t*-tests (two-tailed) revealed that accuracy for all components of the non-verbal format was at control levels while accuracy in the picture–word format was impaired in the patients with PPA but only for the match [$t(28) = 4.71$, $P < 0.001$] and related mismatch conditions [$t(28) = 4.11$, $P < 0.001$]. These results indicate that the patients were selectively challenged in recognizing the word that denoted the object and differentiating it from a word denoting a taxonomically related, but not unrelated, item. The differential performance in detecting related versus unrelated mismatches

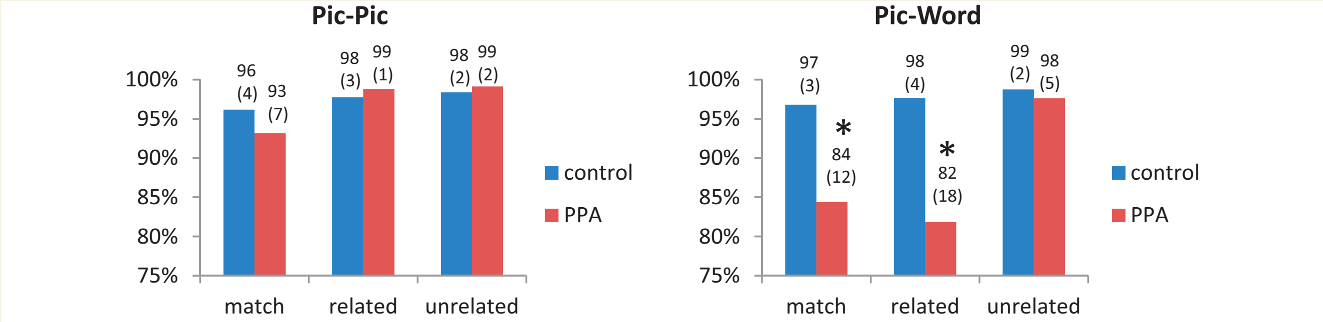

Figure 8 Taxonomically graded object association task. Accuracy on the picture–picture (Pic–Pic) and picture–word (Pic–Word) formats. Numbers on top of bars indicate mean accuracy (SD). Asterisks indicate significant differences at $P < 0.05$.

was significantly greater in PPA than control subjects, but only in the picture–word format, showing that the abnormal taxonomic interference is selective for the verbal associations of objects.

Discussion

The only structural brain abnormality common to all 11 patients in this study was the exclusive or predominant location of peak atrophy within the left anterior temporal cortex. Within these peak atrophy sites, cortical volume was 53–64% less than control values whereas average volume elsewhere in the left hemisphere maintained, on average, 92% of control values. The goal of this investigation was to explore the spared and impaired aspects of word and object knowledge associated with this relatively focal neuronal loss at the tip of the left temporal lobe. When tested with a comprehensive battery used for the quantitative characterization of PPA, all patients displayed a major impairment of object naming on the Boston Naming Test. In three patients, this was the only conspicuous abnormality. Such isolated emergence of anomia in patients with atrophy confined to the anterior tip of the left temporal lobe has been reported previously and found to represent a prodromal stage of semantic PPA in some, but not all, cases (Czarnecki *et al*., 2008; Mesulam *et al*., 2012). The remaining eight patients also displayed major word association and comprehension impairments as revealed by the PPVT, a result that agrees with a previous study on a more heterogeneous group of PPA patients with and without anterior temporal atrophy, where PPVT performance was most strongly correlated with atrophy of the left anterior temporal lobe (Rogalski *et al*., 2011). Non-verbal object associations appeared relatively spared. For example, performance in at least one test of non-verbal object knowledge exceeded the 90% level of accuracy in 5 of 11 patients. The only subject with <80% accuracy in both non-verbal object association tasks, Patient S11, also displayed the most bilateral temporal atrophy. The one patient with prominent impairments in both grammaticality and repetition, Patient S5, was also the only subject to display a small, but significant, patch of additional atrophy in the temporoparietal junction, including the posterior tip of the superior temporal gyrus. Although the assessment of word and object knowledge was not done with identically modelled tasks, the patterns of impairment and relative sparing in Figs 5–7 suggest that the left anterior temporal lobe is more critical for the integrity of verbal than non-verbal associations of objects. The NOMINA and the Taxonomically Graded Object Association Task strengthened this conclusion with more equivalent assessments of verbal and non-verbal impairments underlying the anomic errors.

Mechanisms of anomia: troubleshooting with NOMINA

The classification of the 140 naming errors on the NOMINA showed that the anomias of left anterior temporal atrophy could be attributed to mechanisms that ranged from pure retrieval deficits to complex associative errors, and that the associative errors were more likely to reflect a perturbation of word than of object representations.

Anomias caused by pure retrieval failures

We used a particularly rigorous definition of retrieval anomia. Naming errors fit this classification only if the unnamed object as well as the word denoting the object had been accurately defined and also if the two had been accurately matched to each other on two separate pointing tasks. Pure retrieval anomias accounted for 25% or more of all naming failures in six of the nine patients for whom all relevant data were available. Investigations on semantic dementia have tended to attribute the naming failures in patients with anterior temporal lobe atrophy to impaired general knowledge of the object rather than a specific impairment of verbal retrieval (Snowden *et al*., 1989; Lambon Ralph *et al*., 2001; Adlam *et al*., 2006). Our results show that a substantial number of anomic errors for relatively common objects in patients with predominantly left temporal tip atrophy can actually arise from pure lexical retrieval impairments despite the preservation of the relevant word and object knowledge.

Pure retrieval anomia occurred in the presence of a putative object–word interface that appeared functional enough to support the accurate matching of the unnamed object to its name during the pointing tasks. However, this functionality appeared to be only partially preserved, as it could not support the computationally far more demanding task of searching the vast internal thesaurus [this term is used instead of 'lexicon', in keeping with the usage introduced by Warrington (1975)] and selecting the correct noun for subsequent phonological encoding. Pure retrieval anomia is arguably the single most common type of naming failure seen in neurological disease. It has been described in patients with dysfunction in Brodmann area 37, inferotemporal cortex and several other regions of the left hemisphere (Benson, 1985; Grossman *et al*., 2004; DeLeon *et al*., 2007; Antonucci *et al*., 2008; Rohrer *et al*., 2008). The current study shows that the left anterior temporal cortex can be added to this list of areas that mediate the search and selection of verbal labels for objects, a processing step that appears closely related to the lemma of lexicosemantic models (Indefrey and Levelt, 2004; Schwartz *et al*., 2009).

Associative anomias and interpretation of object knowledge

Naming errors were considered associative if the picture of the unnamed object or the word that represented its name could not be defined verbally, or if the two could not be matched accurately in at least one of two pointing tasks. Pure interface anomias, where object and word were both defined but not matched, were very rare. The vast majority of associative anomias occurred in conjunction with failures to define the word or the object. Inaccurate verbal definitions of words provide reasonably reliable indicators of impaired word knowledge because the input and output stages of the task are both confined to the language network. The verbal definition of object pictures, however, is dependent not only on access to object representations but also on the integrity of the language network needed to mediate the transcription of non-verbal concepts into a verbal account. In patients with language impairments, inaccurate verbal definitions of objects may therefore over-emphasize the loss of object knowledge. This point was anecdotally illustrated by a patient with semantic PPA who was visited at her home and found capable of making appropriate use of objects similar to those she could not name or define during her clinical evaluation (Mesulam *et al*., 2009).

Despite this potential overestimation of impairment when object knowledge is assessed by verbal responses, the percentage of anomias associated with word definition (i.e. comprehension) failures was significantly higher than the percentage associated with object definition failures. Object knowledge impairments therefore appear to play a distinctly less causative role than word comprehension impairments in the associative naming failures that follow left anterior temporal lobe atrophy. This interpretation is in keeping with the generally successful performance of the patients on non-verbal tasks of object knowledge such as the Pyramids and Palm Trees and our Category Matching Test and their successful everyday use of objects. The argument could be advanced that pictured objects are easier to recognize because the shape of the object contains clues related to its function through the phenomenon of affordance (Hodges *et al*., 2000). By the same token, however, one could argue that deciphering the information conveyed through affordance is part of the non-verbal knowledge of the object. The argument has also been advanced that object knowledge failures in this group of patients can only be detected when tested with unfamiliar items. However, it would seem that object knowledge is an experientially acquired faculty that should be tested with items that the subject has used and encountered frequently, not with items that may predominantly elicit encyclopaedic, and therefore verbal rather than experiential, associations.

Taxonomic interference and the architecture of lexicosemantic mapping

In the chronometric task of the NOMINA, the subjects had to match a word to one of two objects of the same or different taxonomic categories. The slowing of reaction times during trials where the correct choice and the foil both belonged to the same category offered a measure of the magnitude of taxonomic interference. As expected, the control as well as the PPA group showed significant interference effects. In six of the PPA subjects, however, the magnitude of this effect was beyond the range seen in the control group. Five of these six patients were also those with the most severe anomia and the greatest failure rates in defining the noun denoting the object they could not name. The Graded Object Association Task confirmed the presence of an abnormally intense interference effect in the PPA group and also demonstrated its selectivity for verbal rather than non-verbal associations of objects.

A previous experiment, based on event-related potentials elicited by our Graded Object Association Task, offered an alternative demonstration of this phenomenon with a paradigm that required no verbal responses (Hurley *et al*., 2012). In this type of experiment (where a picture prime is followed by a matching, related or unrelated probe), the probe normally evokes a neural response that peaks in ~400 ms (N400) and that is larger if it represents a related or unrelated mismatch. The magnitude of the differential N400 elicited by the matching versus mismatching probes can be used to measure the acuity with which taxonomic distances are resolved. In particular, the differential N400 elicited by the unrelated match reflects the sensitivity to the generally more robust inter-category boundaries whereas the differential N400 elicited by the related mismatch reflects the sensitivity to the more fragile intra-category boundaries where the conflict between activation and inhibition is more pronounced. When investigated with this approach, patients with semantic PPA displayed a significant N400 potential in response to the unrelated mismatch but not in response to the related one. Additional analyses showed that this blunting of intra-category distinctions in the N400 response was selectively correlated with atrophy at the tip of the left but not right temporal lobe. This N400 abnormality was not present in a parallel non-verbal part of the experiment where object pictures were matched to other object pictures.

It appears, therefore, that left anterior temporal lobe atrophy leads to an excessive blurring of intra-category compared with inter-category boundaries, but predominantly in selecting verbal associations of objects. It is as if the acuity of word–object associations has been diminished (or as if the grain of representation has become coarser) so that words are easier to understand and link to objects at the generic than at the specific levels of representation. This abnormality provides a potential mechanism underlying object naming and word comprehension failures caused by left temporal tip atrophy and also explains the preponderance of semantic paraphasias, superordinate identification errors and coordinate mispointing tendencies that have been reported repeatedly in patients with anterotemporal atrophy and clinical features of semantic dementia (Snowden *et al*., 1989; Hodges *et al*., 1992; Jefferies and Lambon Ralph, 2006). As temporal lobe atrophy and disease severity increase, word comprehension is likely to become compromised even at the generic level, at which time the excessive taxonomic interference effect may paradoxically disappear, as inter-category boundaries become just as blurred as intra-category boundaries (Mesulam *et al*., 2009).

Category specificity of lexicosemantic deficits for natural kinds versus artefacts, frequently reported in patients with semantic dementia (Warrington and Shallice, 1984; Humphreys and Forde, 2001; Zannino *et al*., 2006), was not detected in the present study. Greater impairment in naming natural kinds has specifically been attributed to dysfunction of anteromedial temporal cortex because of this area's special role in fine-grained discriminations of object concepts and the greater importance of fine-grained discriminations for the category of natural kinds where individual members are more confusable (Bright *et al*., 2005). A previous experiment with NOMINA found greater intra-category blurring for natural kinds in patients with semantic PPA with somewhat more extensive and bilateral peak atrophy sites that spread further into the parahippocampal, inferotemporal and fusiform gyri than in Patients S1–S11 (Mesulam *et al*., 2009). The absence of category specificity in the current study may thus reflect the paucity of major peak atrophy sites in these basomedial parts of the temporal lobe.

Amodality versus domain specificity at the tip of the left temporal lobe

The concept of an 'amodal semantic hub' located at the anterior temporal lobe has received a great deal of attention in the recent literature on semantic dementia and has shaped current thinking on how knowledge might be organized in the brain. The concept has been articulated most succinctly in the following words:

> '. . . the neural network for semantic memory requires a single convergence zone or hub that supports the interactive activation of representations in all modalities, for all semantic categories . . . damage to the hub should produce a semantic impairment that is independent of the modality of input (objects, pictures, words, sounds, tastes and so on) and of the modality of output (for example, naming an object, drawing it or using it correctly)' (Patterson *et al*., 2007).

According to our results, however, the left anterotemporal tissue that was lost in each patient, accounting for at least half of the presumed original cortical volume at the sites of peak atrophy, could not have contained such a unitary repository of amodal semantic memory. If the lost neurons had contained this type of repository, and if it the term 'amodal' is interpreted to designate a domain-independent integration of semantic information, non-verbal and verbal object representations would have been expected to display comparable impairments. This is not what was observed. We obviously cannot rule out the possibility that the surviving anterotemporal neurons in Patients S1–S11 might contain an amodal hub though it is unlikely that the neurodegenerative process in these patients would have selectively destroyed the neurons that lack such amodal properties. Although the proposal has been made that the amodal semantic hub may actually reside in the anterior fusiform gyrus, which was not a major site of peak atrophy in most of our patients, there are also cogent reasons for questioning such a location (Snowden *et al*., 2004; Mion *et al*., 2010).

An alternative conceptualization, based on the classic lesion-induced dissociations between aphasia and object agnosia, invokes two separate, but interactive, routes of processing in the temporal lobes—a strongly left-dominant temporosylvian network for verbal concepts and a presumably more bilateral or right-sided inferotemporal/fusiform network for pictorially triggered object concepts (Damasio, 1985; Mesulam, 1998). The strong left hemisphere concentration of tissue loss and the paucity of peak atrophy sites in the fusiform gyrus could therefore account for the selectivity of the verbal impairments in our patients. According to the two-route account, hubs of the language and object networks would have to interact with each other through reciprocal connections to enable object naming. Such cross-network interactions are likely to have a distributed organization without necessarily relying on a single amodal area of domain-independent confluence. A similar architecture exists in the realm of spatial attention where three transmodal hubs, posterior parietal cortex, frontal eye fields and cingulate gyrus, provide a distributed interactive network that does not appear to require an additional amodal convergence zone for spatial knowledge (Mesulam, 1999). In this kind of model, network hubs have a 'transmodal' architecture where multi-modal (though not pan-modal) convergence does take place but in the presence of domain-specificity, and where inter-network integration is more distributed than confluent (Mesulam, 1990, 1998). In this context, the term 'transmodal' was introduced to collectively designate constituents of the heteromodal, paralimbic and limbic cortical zones (Mesulam, 1998). Transmodal areas receive input from the highest synaptic levels of sensory-fugal processing hierarchies. They have no consistent modality selectivity but display distinct domain specificities and serve as hubs of neurocognitive networks.

In partial support of the two-route account, recent investigations of semantic dementia and patients with unilateral anterior temporal lesions have, in fact, revealed functional asymmetries in the contributions of each anterior temporal lobe to verbal versus non-verbal processing domains (Lambon Ralph *et al*., 2010; Mion *et al*., 2010). Such asymmetrical domain selectivity would presumably constitute a deviation from strict amodality. Temporal lobe lesions may therefore appear to generate domain-independent amodal impairments that equally disrupt verbal and non-verbal components of semantic memory only if they are large and bilateral enough to include the language network together with the inferotemporal/fusiform object recognition network. Semantic memory itself may not represent a unitary function that can be localized but, instead, the collective and interactive contributions of more fundamental networks, each of which contains modality-selective synaptic hierarchies and domain-specific transmodal hubs that mediate the integration and binding of distributed information (Damasio, 1989; Mesulam, 1998, 2008; Martin, 2007; Cappa, 2008).

Implications for nosology

Although this study is not about semantic PPA or semantic dementia, it should be pointed out that the semantic variant of PPA, in fully developed or possibly prodromal form, was detected in 7 of 11 patients and comprised the single largest diagnostic group. The semantic PPA and semantic dementia designations refer to a family of neurodegenerative syndromes characterized by selective atrophy of the anterior temporal lobes. The underlying neuropathology most frequently belongs to a subtype of frontotemporal lobar degeneration characterized by abnormal deposits of the transactive response DNA-binding protein 43 (Rohrer *et al*., 2010). There is, however, considerable interindividual heterogeneity in the location of initial peak atrophy sites and the trajectory of progression. In some cases, as in those presented in this article, peak atrophy sites are initially located predominantly in the left anterior temporal lobe and give rise to a clinical syndrome that fulfils the core PPA criteria. In other cases, the atrophy is more bilateral and gives rise to the combined impairments of language and object recognition that fulfil the Neary *et al*. (1998) criteria for semantic dementia. In still others, the atrophy is mostly in the right hemisphere or in inferior temporal cortex, giving rise to progressive associative prosopagnosia and object agnosias (Tyrrell *et al*., 1990; Snowden *et al*., 2004). As the atrophy progresses, all patterns converge toward combined aphasic and agnosic impairments, collectively attributed to a core semantic deficit (Gainotti, 2012). Depending on the patients that have been selected and the stage of disease, characterizations of semantic PPA and semantic dementia may therefore vary substantially from one study to another. Close attention to the anatomy of atrophy in the individual patient at the time of the neurocognitive evaluation may help to resolve apparent inconsistencies in nosology, and to further clarify the functionality of anterior temporal neocortex.

Conclusion

In his preface to the *Dictionary,* Johnson felt compelled to write, 'I am not yet so lost in lexicography as to forget that words are the daughters of earth, and that things are the sons of heaven' (Johnson, 1755). Had Johnson used the term 'semantics' instead of 'lexicography' his statement would have summarized the main message of the present investigation. Words, as Johnson implied, are culturally invented arbitrary symbols, made to signify whatever the ambient culture dictates, whereas objects have immutable sets of prototypical features that are intrinsic to the essence of the species they represent. Just as the same object goes by different names in different languages, the same noun (e.g. compass) may denote two completely different species of objects. It stands to reason that the two realms of representation, those of the object as object ('a rose is a rose is a rose is a rose') and those of the word as symbol ('a rose by any other name would smell just as sweet'), are likely to be subserved by two separate and dissociable, though interactive, networks. The interactions are necessary since the attributes of the object endow the word with part of its given meaning at the same time that the word is one of the numerous secondary (e.g. acquired rather than innate) associations of the object.

The current results strengthen this separation of functional realms by emphasizing the selective impact of left temporal tip atrophy on the integrity of verbal rather than non-verbal representations of objects. The consequences of neuronal loss in this area include severe anomia, semantic paraphasias and word comprehension impairments in the absence of equivalent perturbations in the non-verbal components of object concepts. These conclusions are in keeping with functional imaging experiments that have demonstrated the activation of the left anterior temporal lobe in tasks of synonym identification (Gitelman *et al*., 2005), and in tasks that require high levels of taxonomic specificity during lexical retrieval (Damasio *et al*., 1996; Grabowski *et al*., 2001). They are also in keeping with anatomically constrained magnetoencephalography, which has revealed an anterior temporal supramodal convergence area involved in word comprehension (Marinkovic *et al*., 2003). Our results are particularly concordant with a study on post-stroke patients that attributed a specific and critical role of the left anterior temporal lobe in mediating fine-grained taxonomic distinctions during the retrieval of object names and which showed that this role was not dependent on amodal pre-lexical conceptualization impairments (Schwartz *et al*., 2009; Walker *et al*., 2011). Despite considerable challenges that face the interpretation of clinicoanatomical correlations in neurodegenerative diseases, the current results suggest that at least parts of the left anterior temporal neocortex should be inserted into the temporosylvian language network where they are likely to play critical roles in linking words to their object referents and in sharpening the taxonomic acuity of naming and word comprehension.

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